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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,965	01/11/2002	Xian Chen	S-94,799	6404
35068	7590	05/11/2004	EXAMINER	
UNIVERSITY OF CALIFORNIA LOS ALAMOS NATIONAL LABORATORY P.O. BOX 1663, MS A187 LOS ALAMOS, NM 87545			GITOMER, RALPH J	
			ART UNIT	PAPER NUMBER
			1651	

DATE MAILED: 05/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/043,965	CHEN, XIAN	
	Examiner	Art Unit	
	Ralph Gitomer	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 January 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-33 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-33 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

The point of novelty which has been searched and considered here is identifying a protein by performing mass spec on the digested protein, and also performing mass spec on another sample of the same protein where 100% of at least one single specific amino acid is stable isotopically labeled. A comparison of the masses of the peptides generated from proteolytic digestion of the residue specific labeled protein with those of an unlabeled control assists in identifying the mass tagged peptides by monoisotopic resolution. Methods of such isotopical specific labeling are known. Priority is claimed to 1/11/2002.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 7-9, 11-13, 15-18, 23-26, 28-30, 32, 33 are rejected under 35 U.S.C. 102(a) as being anticipated by Franza.

Franza (6,653,076) entitled "Stable Isotope Metabolic Labeling for Analysis of Biopolymers" with a 102(e) date of 3/9/2000, teaches in column 3, a labeled probe is incorporated into the new polymer and isolated, cleaved, and isotopic peaks determined with mass spec. For each fragment, the relative abundance of the different mass peaks from samples containing probe is compared to the mass peaks from samples where the probe is absent. In column 5, Fig. 2 shows peptides containing identical amino acid

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sequences but with one of the amino acids fully substituted with ^{15}N . Mixtures of unsubstituted and substituted spectra are shown. Figs 3A-C show mass peak distribution from a sample grown in the presence of ^{15}N -isoleucine and ^{15}N -leucine. In column 6 lines 42-44, the relative abundance of monoisotopic mass peaks are shown. In column 7, first paragraph, isotopically labeled components can be distinguished from non-labeled components. Preferably more than 98% is enriched with the stable isotope. See the claims.

All the features of the claims are taught by Franza for the same function as claimed.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 2-6, 10, 14, 19-22, 27, 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Franza in view of each of Waugh and Veenstra.

Franza (6,653,076) entitled "Stable Isotope Metabolic Labeling for Analysis of Biopolymers" with a 102(e) date of 3/9/2000, teaches in column 3, a labeled probe is incorporated into the new polymer and isolated, cleaved, and isotopic peaks determined with mass spec. For each fragment, the relative abundance of the different mass peaks from samples containing probe is compared to the mass peaks from samples where the

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probe is absent. In column 5, Fig. 2 shows peptides containing identical amino acid sequences but with one of the amino acids fully substituted with ^{15}N . Mixtures of unsubstituted and substituted spectra are shown. Figs 3A-C show mass peak distribution from a sample grown in the presence of ^{15}N -isoleucine and ^{15}N -leucine. In column 6 lines 42-44, the relative abundance of monoisotopic mass peaks are shown. In column 7, first paragraph, isotopically labeled components can be distinguished from non-labeled components. Preferably more than 98% is enriched with the stable isotope. See the claims.

The claims differ from Franza in that they recite the limitation of the labeled amino acid in the protein is produced by *E. coli*. Specific amino acids are recited in claims 6, 22. Claims 10, 27 are directed to liquid chromatography. Claims 14, 31 are directed to a confirmation step.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to select any desired amino acid to label in view of Franza because Franza selects two amino acids as examples and the labeling of amino acids as desired is well known in this art. No criticality is seen for the presently claimed selection.

Regarding claims directed to chromatographic methods of isolation or separation, the references cited herein disclose known methods of chromatography for the same function as presently claimed. No criticality is seen in the selection of any known chromatographic technique for its known function with the expected result.

Regarding a confirmation step, no novelty is seen in view of the state of the art in mass spec regarding controls and confirmation.

Waugh (J of Biomolecular NMR) entitled "Genetic Tools for Selective Labeling of Proteins with Alpha 15N Amino Acids" teaches in the abstract, E. coli are cultivated to produce residue specific labeling of proteins.

Veenstra (Am Soc for Mass Spec) entitled "Proteome Analysis Using Selective Incorporation of Isotopically Labeled Amino Acids" teaches in the abstract, identifying proteins by performing mass spec on proteins produced by E. coli with natural isotopic abundance and isotopically labeled specific amino acids such as Leu-D10.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the method of making the isotopically labeled protein with E. coli as shown by each of Waugh and Veenstra in the method of Franza because Franza teaches isotopically produced proteins by cells in general or they are available commercially. To employ a known method of producing labeled proteins with E. coli with the expected result would have been obvious because employing any known method of making the labeled proteins would have the expected result.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 14, 16, 18, 23, 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Each of the following applies in all occurrences.

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In claim 2(a) "capable of" is indefinite regarding what actually occurs. In claims 16, 33 "the proteome" lacks antecedent basis. In claims 18, 23 "a chosen amount" may be intended to be "a selected amount" to be more proper.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Tang (6,393,367) teaches protein identification.

Aebersold (6,670,194) entitled "Rapid Quantitative Analysis of Proteins or Protein Function In Complex Mixtures" teaches isotopically labeled linkers.

Tarr (5,824,556) teaches protein mass spec techniques.

Jensen (Rapid Comm in Mass Spec) teaches delayed extraction MALDI for protein identification.

Quadroni (Proteomics) entitled "Enhancing High Throughput Proteome Analysis: The Impact of Stable Isotope Labeling", no exact currently available, teaches on page 154, In vivo specific labeling. This allows one to differentiate between the peptides originating from two cell pools.

Rose (Biochem J) teaches isotopically labeled carboxy groups liberated during enzyme catalyzed partial hydrolysis of the protein.

Qin (Rapid Comm in Mass Spec) teaches peptide sequencing with ^{18}O labeling.

Shevchenko (Rapid Comm in Mass Spec) teaches isotopic labeling of digested peptides.

Hillenkamp (Anal Chem) teaches MALDI with proteins.

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Chait (6,391,649) with a 102(e) date of 5/1999, entitled "Method for the Comparative Quantitative Analysis of Proteins and Other Biological Material by Isotopic Labeling and Mass Spectroscopy" teaches in column 3 last two paragraphs, a first sample of material is cultured in a medium containing a natural abundance of isotopes and a second sample is cultured in a second medium containing more or less than the natural abundance of one or more isotopes. A removed protein which may be digested into peptides is subjected to mass spec. In column 4 line 42 proteins are shown. In column 7 lines 24-25, the proteins subjected to the mass spec are identified. See the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ralph Gitomer whose telephone number is (571) 272-0916. The examiner can normally be reached on Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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